

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

Isenbruck | Böst | Hühner | or |
Wichmann | Hühner, Patentanwälte
see form PCT/ISA/220 860 880
D-81535 München

10. Dez. 2004

Frist:
Vorfrist:

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220			FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/EP2004/007679	International filing date (day/month/year) 12.07.2004	Priority date (day/month/year) 10.07.2003	B1	
International Patent Classification (IPC) or both national classification and IPC A61K39/00, A61K39/002, A61K39/02, A61K39/12, A61K39/295, A61K39/35, A61K39/36, A61P37/04			B2	
			B3	
			Sekr	
			EDV	
Applicant CYTOS BIOTECHNOLOGY AG			Ablg.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Schulz, R

Telephone No. +31 70 340-4381



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/007679

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☐ claims Nos. 57-59, 61, 62 with regard to industrial applicability

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 57-59, 61, 62 with regard to industrial applicability
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/007679

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	23 - 25
	No: Claims	1 - 22, 26 - 63
Inventive step (IS)	Yes: Claims	
	No: Claims	23 - 25
Industrial applicability (IA)	Yes: Claims	1 - 56, 60, 63
	No: Claims	57 - 59, 61, 62

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1) Claims 57 - 59, 61 and 62 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 03/024481 A (Bachmann et al.)

D2: Schwarz, K. et al. (2003) Role of toll-like receptors in costimulating cytotoxic T cell responses. J. Immunol. 33(6), 1465 - 1470.

V.2 NOVELTY (Art. 33(1)(2) PCT)

V.2.1 The present application does not meet the criteria of Art. 33(1) PCT because the subject-matter of claims 1 - 22 and 26 - 63 is not new in the sense of Art. 33(2) PCT.

V.2.2 D1 discloses compositions comprising virus like particles (VLPs) for prophylactic or therapeutic vaccination against allergies, tumors and other self-molecules and chronic viral diseases. These compositions comprise an antigen, preferably a recombinant antigen and immunostimulatory unmethylated CpG-containing oligonucleotides which preferably are stabilised by phosphorothioate modifications of the phosphate backbone. The VLP is preferably a recombinant one and free of a lipoprotein envelope (p. 9, l. 4 - p. 13, l. 12). D1 also refers to molecules activating toll-like receptors (TLRs) (p.60, last para - p. 61, 1st para).

- V.2.3 The study described in D2 was aimed to assess the ability of TLR molecules other than TLR9 to enhance CTL responses upon vaccination. The hepatitis B core antigen containing the CTL epitope 33 was used as a model antigen p33-VLP and the ability of different TLR ligands to enhance VLP-induced CTL responses was assessed (Table 1, Fig. 1), i.e. ligands of TLR2, 4 and 9 (p. 1467 left-hand side column, l. 11 - 15). In addition, several oligonucleotides (Fig. 2; p. 1469, left-hand side column, 3rd para) were used in order to test whether the enhancement of CTL response was a property of a particular CpG.
- V.2.5 D3 discloses immunostimulatory nucleic acid compositions, e.g. those comprising oligonucleotides having the same general formula as those of the present application (p. 7, l. 8 - 13, Table A: SEQ ID NO: 1071, SEQ ID NO: 1075, p. 59).
- V.2.6 Subject-matter of claims 23 - 25 appears to be novel and to meet the requirements of Art. 33(2) PCT, since neither of the prior art documents discloses an oligonucleotide as referred to in said claims:
the immunostimulatory unmethylated CpG-containing oligonucleotide referred to in D1 (claim 21 (d)) differs in that its palindromic sequence is flanked by 10 guanosine entities at its 5' as well as at its 3' terminus instead of at least 4 and at most 9 at the 5' terminus and of at least 6 and at most 9 guanosine entities at the 3' terminus.

V.3 INVENTIVE STEP (Art. 33(1)(3) PCT)

- V.3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of 1 - 22 and 26 - 63 is not new in the sense of Art. 33(2) PCT (see above) and subject-matter of dependent claims 23 - 25 is considered as not to involve an inventive step in the sense of Art. 33(3) PCT.
- V.3.2 The document D1 is regarded as being the closest prior art to the subject-matter of claims 23 - 25 and discloses compositions comprising VLPs used in vaccination and comprising immunostimulatory nucleic acid molecules as well as further antigens (see above).

- V.3.3 The subject-matter of claims 23 - 25, i.e. immunostimulatory unmethylated CpG-containing oligonucleotides, differs from the ones disclosed in D1 (i.e. claim 21 (d)), in that its palindromic sequence is flanked of at least 4 and at most 9 guanosine entities at its 5' terminus and of at least 6 and at most 9 guanosine entities at the 3' terminus instead of 10 guanosine entities at the 5' and 3' terminus as in D1 (cf. claim 21(d)).
- V.3.4 The problem to be solved by the present invention may therefore be regarded as the provision of an alternative immunostimulatory unmethylated CpG-containing oligonucleotide.
- V.3.5 The solution proposed in dependent claims 23 - 25 of the present application cannot be considered as involving an inventive step in the sense of Art. 33(3) PCT because the constructional change in the immunostimulatory unmethylated CpG-containing oligonucleotide of said claims is considered as to come within the scope of the customary practice followed by persons skilled in the art. The subject-matter of said claims consists in the selection of a number of guanosine entities flanking the palindromic sequence from the range of 2 - 10 and 7 - 10 known in the art, e.g. D1 (claim 21) and D3 (Table A, p. 59, SEQ ID NO: 1071 and SEQ ID NO: 1075). Such a selection can only be regarded as inventive, if the deletion of a Guanosine entity at the 5' and 3' terms presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 23 -25.

V.4 COMMENT

- V.4 For the assessment of the present claims 57 - 59, 61 and 62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/007679